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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,980	02/14/2001	Michael Eisenhut	41443	9550

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application N .	Applicant(s)	
	09/781,980	EISENHUT ET AL.	
	Examin r	Art Unit	
	J. Douglas Schultz	1635	

--Th MAILING DATE of this communication appears on the cov r sh et with th correspondenc address --

THE REPLY FILED 22 September 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: *See Continuation Sheet*.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-13, 15-17 for reasons of record*.

Claim(s) withdrawn from consideration: *14*.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Continuation of 2. NOTE: Applicants' amendment identifies claims drawn to an oligonucleotide and a somatostatin analog, wherein said amendment now recites that the oligonucleotide and somatostatin anolog are conjugated by one or more covalent bonds. While a narrower limitation has been searched, wherein the oligo is conjugated to the somatostatin analog at the 5' end, a search has not been performed on conjugation of the somatostatin at any position on the oligonucleotide, wherein said conjugation may comprise one or more covalent bonds. Such an amendment, if entered, would require new considerations due to the newly claimed aspect of covalent bond formation at any point on the molecule which had not been previously examined, and would necessitate a new search. Accordingly, entry of applicants' amendment is denied..

Continuation of 5. does NOT place the application in condition for allowance because: applicants arguments are not considered convincing.

Applicants' declaration has been considered. The reference of Wu, alleged to be submitted with the request for reconsideration, has not been found. However, a copy located by the examiner has been reviewed. These documents are not considered to support applicants arguments for the following reasons. Applicants declaration emphasizes a showing that the somatostatin/oligo conjugate binds to its somatostatin receptor (SSTR) better than the somatostatin analog of Nagy alone. Since the enablement rejection never set forth or relied upon a presumption that the conjugate of Nagy binds its target better than applicants' conjugate, it is not clear from such evidence or from applicants arguments what the relevance of such a comparison is. The somatostatin molecule of Nagy is conjugated to a completely different molecule than that of the instant application, and would not be expected to have identical binding profiles. If applicants intention is to show that one of ordinary skill in the art would not expect to successfully use the concept of Nagy's conjugates to target somatostatin bearing cells as instantly claimed, this contention would not be adopted, since there is no reason to doubt that the data of Nagy et al. is not sound. Because Nagy show success in making and using such conjugates, one of skill would have a reasonable expecatation of success in making and using similar conjugates.

Furthermore, the assertion that the data contained in the instant declaration show a greater success than would be expected from the conjugates of Lu, applicants have provided no basis for making such comparison. Any data in the declaration that may support such an assertion cannot be found, and furthermore, even if it could be found, would be of questionable value since the molecules of Lu and the instant application differ; thus, one of ordinary skill would not expect to be able to reliably compare data between the two, since each is expected to have its own unique target expression profile and distribution, and its own target affinity. Regarding applicants' data showing that the instantly claimed compound is taken up by cells, this is not in dispute. However, the claims are drawn to methods of treatment, and applicants' data and specification does not show any treatment effect in an host-analogous model system. In fact, applicants data showing increased accumulation of antisense in target cells does not show any indication of target inhibition in any manner. Therefore, these data are not considered to support claims drawn to treatment in hosts in need thereof.

Applicants further cite several pre and post-filing references and clinical trials to support the claim of enablement, and assert that "prediction of efficacy is not within the purview of the USPTO". This last statement is clearly in error. Applicant is reminded that in order for applicants' invention to be enabled, one must be able to make and use the invention commensurate with the claimed scope. This requires some degree of predictabiltiy. If the Office could not require any prediction of efficacy as stated by applicant, then the office would have no standing to require that one provide a disclosure sufficient to enable the public to make and use a claimed invention. Unpredictability is a fundamental evaluation in the analysis of enablement. See MPEP 2164. Finally, although applicants argue that numerous clinical trials have been initiated using antisense molecules, post filing references are not considered convincing evidence of enablement, since the invention must be enabled at the time of filing. See MPEP 2164. Regarding those citations of clinical trials at or before applicants filing date, it is noted that only one clinical trial of any antisense compound has ever proceeded to FDA approval. However, even this compound is not considered typical of any antisense molecule, because it works only through injection directly into the eye, which bypasses immunogenic, concentration and localization concerns raised in the enablement rejection. The remainder of applicants cited clinical trials have either failed and dropped out of testing altogether, or are still in testing and not approved. For these reasons, applicants arguments drawn to such clinical trials are considered unconvincing.

Applicants arguments that the compound claims are not obvious over the prior art are similarly unconvincing. Applicants argue that one would not have a reasonable expectation of success in making and presumably using such compounds, because Nagy et al. teach that their conjugates exhibited a lower binding profile than the unconjugated somatostatin. Applicants reason that since the instantly claimed conjugates involve nucleotide sequences which are larger, that this would be expected to result in a greater decrease in binding affinity. However, applicant has provided no basis for asserting this expectation. To the contrary, it may be that the larger molecule stablizes the somatostatin binding. Without any empirical indication either way, applicants assertions are unsubstantiated and thus unconvincing.

Applicants further assert that the Lu reference depends on the teachings of Wu, which teaches away from the claimed invention because Wu includes a complexed cation not presently claimed, and because Wu states that covalent bonding of the conjugate moieties would damage the DNA. Regarding this latter point, applicants have cited a specific passage from Wu which simply does not teach or suggest the interpretation of applicants, and in fact is not related in any way. Applicants are invited to clarify. Finally, regarding the presence of a complexed polycation in Wu, it is maintained that the inclusion of an extra element in the prior art combination, i.e. the polycation, does not render the instant conjugate unobvious. See mpep 2144.04(II)(A): "Omission of an element and its fundtion is not obvious if the function of the element is not desired."

No claims are allowed.

SEAN McGARRY
PRIMARY EXAMINER